REMARKS

Initially, Applicant would like to thank the Examiner for granting a telephone interview on December 27, 2004. During the telephone interview, he suggested that Applicant file this second supplemental response to the final Office Action dated August 9, 2004 ("final Office Action"), in view of the first Advisory Action dated October 26, 2004 ("first Advisory Action") and the second Advisory Action dated December 3, 2004 ("second Advisory Action").

In the final Office Action and the first Advisory Action, the Examiner maintained the rejection of claims 33-40, 45, 46, and 51-57, drawn to an expression vector or a related method, as being obvious over Zhang et al., J. Biol. Chem. 270(15): 8501-8505 ("Zhang") in view of one or both of Miller et al., Biotechniqus 7(9): 980-990, 1989 ("Miller") and Jarman et al., Mol. Cell. Bio. 11(9): 4679-4689 ("Jarman"). Independent claim 33 covers a viral expression vector that contains, among others, an enhancer having SEQ ID NO:1 or its complement. Independent claim 51 is drawn to a method of using the expression vector. According to the Examiner, (i) Zhang teaches a non-viral expression vector that has a SEQ ID NO:1-containing HS40 enhancer, (ii) Miller teaches retroviral vectors containing promoters, and (iii) Jarman teaches a regulatory element of the human α globin gene. He proceeded to conclude that it would have been obvious to one skilled in the art to combine all of the cited references to make or use the claimed invention.

In the response to the final Office Action, Applicant rebutted the obviousness rejection by a showing of expected results. In the first supplemental response mailed November 8, 2004, Applicant presented the unexpected results again as a Declaration by Dr. Shen. More specifically, use of the claimed vector, but not a control vector, resulted in "position-independent and copy-number-dependent expression on a transgene in an animal." In addition, the claimed vector drove continued expression of a transgene into adulthood of the animal, while the control vector failed to do so. Applicant further submitted a copy of a non-prior art reference Lung et al., Blood Cells, Molecules, and Diseases, 2000, 26, 613-619.[1] This paper teaches a retroviral

[1] The Lung reference is not prior art as it was published in December 2000, which was more than two years after the effective filing date of the instant application, i.e., October 4, 1998.

vector containing an HS-40 enhancer, N2Aγ(HS-40), which failed to drive expression of a gene operatively linked to the enhancer in an animal.

Nonetheless, in the second Advisory Action, the Examiner countered that Applicant's rebuttal was

> NOT persuasive ... because the invention as claimed is drawn to a retroviral vector encoding a [ζ]-globin enhancer ... that drives the expression of a gene of interest and NOT [drawn to] the intended use of retroviral vector in-vivo, which Lung et al finds resulted in no expression. [Contrarily] to applicant's assertion Lung et al. clearly teaches that a retroviral vector containing an HS-40 enhancer provides high level[s] of in MEL cells ... [and] the declaration by Dr. Shen only teaches transgene expression (mtHS50-zGH) in transgenic mice which does not support applicant[']s assertion that a retroviral vector as claimed is an unexpected finding, especially in view of the fact that a retroviral vector containing an HS-40 enhancer is capable of providing a high level of gene expression in isolated MEL cells (see Lung et al).

See the second Advisory Action, page 3, last paragraph.

The Examiner's ground for rejection, apparently directed to the expression vector of claim 33, can be paraphrased as follows:

(1) Dr. Shen's declaration showed much higher levels of in-animal expression driven by the vector of claim 33 than by the Lung et al. vector;

(2) both the vector of claim 33 and the Lung et al. vector drive high levels of in-cell line expression;

(3) claim 33 is drawn to a vector containing an enhancer that drives gene expression both in a cell line and in an animal, not in an animal only; and

(4) given the above three facts, the in-animal comparative data shown in Dr. Shen's declaration cannot be used to support nonobviousness of claim 33.

In other words, it is the Examiner's position that, although Applicants have shown higher in-animal expression driven by the vector of claim 33 than the Lung et al. vector, he also has to show higher in-cell line expression driven by the vector of claim 33. Applicants disagree.

Indeed, during the above-mentioned telephone interview, Applicant's counsel pointed out that, according to the relevant guidelines from MPEP 716.02(a), as well as *In re Chupp*, 816 F.2d

643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987), the unexpected high-level expression in an animal is enough to rebut a prima facie case of obviousness. The Examiner acknowledged the guidelines and agreed to reconsider this case if another supplemental response was filed.

Applicant files herewith a second supplemental response and recites below the relevant guidelines provided in MPEP 716.02(a) (emphasis added).

> "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) (Evidence showing that the claimed herbicidal compound was more effective than the closest prior art compound in controlling quackgrass and yellow nutsedge weeds in corn and soybean crops was sufficient to overcome the rejection under *35 U.S.C. 103*, even though the specification indicated the claimed compound was an average performer on crops other than corn and soybean.).

In this connection, Applicant would like to point out that the in-animal expression level is "one of a spectrum of common properties" of expression vectors. According to the MPEP, "[e]vidence that [the claimed expression vector] is unexpectedly superior in one of a spectrum of common properties ... can be enough to rebut a *prima facie* case of obviousness." Indeed, just as in *In re Chupp*, "[e]vidence showing that the claimed [expression vector] was more effective than the closest prior art [vector for expression in an animal] was sufficient to overcome the rejection under 35 U.S.C. 103, even though ... the claimed [vector] was an average performer [for expression in a cell line]."[2]

In view of the remarks set forth above, as well as those provided in previous responses, Applicant submits that claim 33 is non-obvious over the cited art. Claim 51 is drawn to a method of using the vector of claim 33. For the same reasons, it is also non-

[2] Lung et al. is a non-prior art reference. Nonetheless, the Lung vector is closer to the claimed vector than those taught in all of the cited prior art references. Since the claimed vector is more effective than the Lung vector in driving in-animal expression, it follows that the claimed vector is also more effective than the closest prior art vector.

obvious. So are the other pending claims, all of which depend from claims 33 or 51 directly or indirectly.

CONCLUSION

Applicant submits that the grounds for the rejection asserted by the Examiner have been overcome, and that claims, as pending, define subject matter that is non-obvious. On this basis, it is submitted that allowance of this application is proper, and early favorable action is solicited.

Enclosed please find a Petition for Two-Month Extension of Time with the required fee of $225. Please apply any other charges to Deposit Account No. 06-1050, referencing Attorney Docket No. 08919-016003.

Respectfully submitted,

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